

Minireview

Congenital anomalies of kidney and hand: a review

Gopalakrishnan Natarajan, Dhanapriya Jeyachandran, Bala Subramaniyan, Dineshkumar Thanigachalam and Arul Rajagopalan

Department of Nephrology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003, India

Correspondence and offprint requests to: Dhanapriya Jeyachandran; E-mail: priyamdhana@yahoo.co.in

Abstract

'Acro-renal syndrome' refers to co-occurrence of congenital renal and limb anomalies. The term acro-renal syndrome was coined by Curran *et al.* in 1972 though Dieker and Opitz were the first to report this phenomenon in three male patients in 1969. The common limb defects include oligodactyly, ectrodactyly, syndactyly or brachydactyly anomalies of the carpal and tarsal bones and the common renal anomalies observed are unilateral renal agenesis (URA), bilateral renal hypoplasia, ureteric hypoplasia, hydroureteronephrosis and duplication abnormalities. The acro-renal syndrome as originally described is rare, reported only in ~20 patients in the international literature. We report a 23-year-old male patient with renal anomalies in the form of absent right kidney, left-sided vesicoureteric reflux (VUR) and skeletal anomalies viz short radius, absent first metacarpal ray in left hand and left undescended testis, consistent with Dieker's type acro-renal syndrome. Apart from the classical acro-renal syndrome, several anomalies of acro-renal patterns and the abnormal gene loci involved are described in the literature. This article is a comprehensive review of the development of kidneys, types of acro-renal syndromes, congenital anomalies of the kidney and urinary tract (CAKUT), syndromes associated with combined limb and renal anomalies, and anomalies associated with URA.

Keywords: acro-renal syndrome; CAKUT; URA; vesicoureteric reflux

Introduction

Limb and urinary tract anomalies have frequently been reported to occur together as components of a single acro-renal defect or multiple malformation syndromes [1]. The incidence of associated limb and renal anomalies is about 1 in 20 000 births. The acro-renal syndrome has a restrictive definition with limb defects usually bilateral, like cleft hands or feet and longitudinal defects involving radius or ulna, tibia or fibula [2]. Renal anomalies include agenesis (unilateral or bilateral), hypoplasia and rarely polycystic kidneys. Additional malformations may involve the oro-mandibular region, the trachea and lungs, skin derivatives including sweat glands, mammary glands, the uterus, vas deferens, the nasal placodes and the eyes. Our patient had left upper limb anomalies viz shortened radius, absent first metacarpal ray (thumb and first metacarpal bone) and absent trapezium and scaphoid carpal bones (Figures 1 and 2), axial skeletal anomalies like scoliosis and sacral hypoplasia (Figures 3 and 4) and renal anomalies (left solitary kidney with grade 5 VUR).

mesonephros, and metanephros that develop in a cranio-caudal fashion [3, 4]. During embryonic development, the pronephros appears in pair towards the cranial end of the intermediate mesoderm. The epithelial cells in this region arrange themselves in a series of tubules and join laterally with the pronephric duct. The pronephric duct induces nearby intermediate mesoderm in the thoracolumbar area to form epithelial tubules called mesonephric tubules which are drained into the continuation of the pronephric duct, now called the mesonephric duct or wolffian duct. During the fifth week of gestation, the mesonephric duct develops an outpouching, the so-called ureteric bud [3]. The elongated stalk of the ureteric bud called the metanephric duct later forms the ureter. The cranial end of the ureteric bud extends into the intermediate mesoderm and undergoes a series of branching to form the collecting duct system. It also forms the major and minor calyces and the renal pelvis. The essential step in the process of kidney development is the mutual induction between the metanephric mesenchyme and the ureteric bud [5]. As the foetus develops, the torso elongates and the kidneys rotate and migrate upward towards the lumbar region.

Embryology of renal tract

The development of the kidney proceeds through a series of successive phases, which include pronephros,

Congenital anomalies of kidney and urinary tract

Kidney malformations occur during organogenesis between 4 and 12 weeks of foetal life leading to congenital



Fig. 1. Clinical photograph showing hypoplastic left forearm with absent thumb. Compare with the normal right upper limb.



Fig. 2. Radiography showing short radius, absent trapezium, scaphoid, first metacarpal and phalanges of thumb.

anomalies of the kidney and urinary tract (CAKUT) [6]. The incidence as detected in antenatal ultrasound examinations is 1:500 [7]. The urinary tract anomalies account for ~20–30% of total congenital anomalies diagnosed during pregnancy [3]. CAKUT is phenotypically variable and results in significant renal problems in adulthood ranging from hypertension, proteinuria to end-stage renal disease [8]. The spectrum of CAKUT includes kidney hypoplasia/dysplasia, renal agenesis, multicystic, horse-shoe or duplex kidneys, VUR, hydroureter, hydronephrosis and obstruction at the vesicoureteric or uretero-pelvic junction [5, 8].

Congenital renal anomalies can be sporadic or familial, syndromic (also affecting non-renal tissues) or non-



Fig. 3. Radiography abdomen showing sacral hypoplasia.



Fig. 4. Lateral abdomen radiography showing vertebral kyphoscoliosis.

syndromic. The primary insults believed to be associated with the development of CAKUT are environmental factors and genetic mechanisms [9, 10]. Animal studies have shown that any perturbations to the foetal environment that include maternal food restriction, low-protein

diet, placental insufficiency, maternal vitamin A deficiency, use of alcohol and drugs like angiotensin-converting enzyme inhibitors and sodium valproate can result in reduced nephron endowment and renal anomalies. Various genetic loci associated with syndromic CAKUT are identified. In animal models, deletion of several of these genes results in low nephron endowment including PAX2, p53, GLI3R, GDNF, FGF 7, FRS2 and Six2 [11, 12]. The UK Renal Registry data show that dysplastic/hypoplastic kidneys together account for ~40% of all children on renal replacement therapy and are six times more common than nephronophthisis, congenital nephrotic syndromes or metabolic diseases [13].

Acro-renal syndrome

The acro-renal syndrome of Dieker's type is sporadic in nature as in our patient. The anomalies include unilateral renal agenesis (URA), ectopic kidneys, urethral diverticulum, hydro ureteronephrosis, ectrodactyly, oligodactyly and hypoplastic carpal/tarsal bones [1, 14]. Acro-renal syndrome of Johnson-Munson is characterized by unilateral or bilateral renal agenesis, aplangy, hemivertebrae and genital or intestinal dysgenesis [15]. The acro-renal syndrome of Siegler is characterized by renal ectopia, hydronephrosis, ureteric atresia, short stature, hypoplastic radii/ulna and oligodactyly [1]. The mode of inheritance and the gene loci involved in acro-renal syndromes remain unclear, but it is believed they follow an autosomal recessive fashion [12]. A candidate gene for acro-renal disorders is the Formin gene that has been mapped to 15q13-14. Renal failure reported in patients with acro-renal syndrome is due to oligomeganephronic renal hypoplasia [16-18], bilateral renal agenesis, secondary focal segmental glomerulosclerosis [2] or other associated urological anomalies.

Syndromes with acro-renal anomalies

The phases of development with respect to kidney and limbs occur in a synchronized manner during the initial 3-8 weeks of gestation. There are a number of syndromes with combined anomalies of the renal system and limbs other than the classical acro-renal syndrome. Such acro-renal defects are clearly heterogeneous in terms of cause and specific morphological defects, but rarely observed without malformations in other systems [19]. Few such conditions are summarized below.

(i) Autosomal dominant inheritance

- (a) Acro-renal-ocular syndrome (AROS) is characterized by ocular anomalies (optic nerve coloboma), radial ray abnormalities of the hand from mild thenar hypoplasia to hypoplastic thumbs or prominent upper limb abnormalities and urinary tract anomalies including URA, renal ectopia, malrotation, bilateral renal hypoplasia, horseshoe kidney, VUR and bladder diverticulum [20, 21]. In addition, sensorineural deafness, cardiac anomalies and anal stenosis are noted. Duane-Radial Ray syndrome allelic to AROS is characterized by Duane eye anomaly, radial ray malformations like triphalangeal thumb, preaxial

polydactyly, hypoplasia/aplasia of the thumb and radii, shortening and radial deviation of the forearm. This is due to mutations in the SALL4 gene in chromosome (chr) 20 q [22].

- (b) Townes-Brocks syndrome is caused by mutation in the putative zinc finger transcription factor gene SALL1 in chr 16q and the features include thumb malformations [23, 24], dysplastic ear, URA, conductive deafness and imperforate anus. The incidence is 1:250 000 live births [25, 26].
 - (c) Pallister-Hall syndrome includes imperforate anus, renal anomalies (renal hypoplasia or agenesis), limb anomalies (polydactyly, short limbs, syndactyly and nail dysplasia) and genitourinary abnormalities (microphallus/cryptorchidism) [27, 28]. This is due to heterozygous mutations in GLI3 (Gli-Kruppel family member 3) in chr 7p [29, 30].
 - (d) Hajdu-Cheney syndrome is characterized by acro-osteolysis, short neck, short stature, coarse face, dental anomalies, renal abnormalities (cystic kidney disease and hypoplastic kidneys), cardiac anomalies, hepatosplenomegaly, hydrocephalus and cleft palate [31, 32].
- (ii) Autosomal recessive inheritance
- (a) Acro-renal-mandibular syndrome is characterized by URA, ectrodactyly and hypoplastic mandible. The pathogenesis is linked to an abnormal epithelial-mesenchymal interaction during embryonic development [33-35].
 - (b) Fraser syndrome: the incidence is 1:200 000 live births and is due to mutations in FRAS1 and FREM2 [36], associated with URA, cryptophthalmos, genital anomalies and syndactyly [37].
 - (c) Short-rib polydactyly syndrome types I and II: cystic dysplasia, hypoplasia of ureters, dwarfism, thoracic dystrophy, polydactyly, syndactyly and short limbs. Molecular basis is yet to be identified [38].
- (iii) Miscellaneous
- (a) VACTERL association is typically defined by the presence of at least three of the following congenital malformations: vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities [39]. This is one of the close differential diagnoses of acro-renal syndrome. The incidence is 1 in 10 000-40 000 live births. Vertebral anomalies typically include segmentation defects, such as hemivertebrae, butterfly vertebrae and vertebral fusions, supernumerary or absent vertebrae. Cardiac malformations are seen in 40-80% [40, 41]. Renal anomalies, which may include URA (or bilateral in severe cases), horseshoe kidney, and cystic and/or dysplastic kidneys, and ureteral anomalies are reported in 50-80%. Limb malformations are seen in 40-50% which include radial anomalies, including thumb aplasia/hypoplasia, polydactyly and lower limb anomalies. Approximately 90% of cases appear to be sporadic. The presumed gene involvement is Shh, Gli, HOXD13 and ZIC3 [40-43].
 - (b) Atrio-acro-renal syndrome [44] of partial trisomy 4q is characterised by mental retardation,

dysplastic ears with large antihelix, anti-mongoloid palpebral fissures, malformations of the fingers and thumb, renal malformations (horseshoe kidney, renal hypoplasia, ureteral reflux with or without hydronephrosis), congenital heart disease and cryptorchidism [44, 45].

- (c) MURCS syndrome: Mullerian duct aplasia, renal aplasia, and cervico-thoracic somite dysplasia (also known as Mayer-Rokitansky-Kuster-Häuser syndrome type II) is associated with vertebral anomalies, anorectal malformation, cardiac and limb anomalies (syndactyly) and hearing loss [46, 47].
- (d) Poland's syndrome: the incidence is 1 in 7000–10 000. Males are affected more frequently (M:F ratio is 3:1) [48–50], commonly involving the right side (60–75%). In addition to aplasia of the pectoralis, major renal anomalies such as URA or duplication of the urinary collecting system are noted [51, 52].
- (e) Anomalies due to toxic and metabolic factors: foetal alcohol syndrome presents with small rotated kidneys, URA, growth retardation, microcephaly, short palpebral fissures, limb and cardiac defects. Renal agenesis/dysplasia, brain, heart and skeletal anomalies, caudal regression syndrome are seen in fetuses of diabetic mothers [53]. Thalidomide embryopathy is characterized by renal agenesis, hypoplasia, horseshoe kidney, cystic dysplasia, renal ectopia, anomalies of rotation, phocomelia, heart, intestinal and genitourinary anomalies [54].

Renal agenesis

Renal agenesis is the most profound renal tract malformation characterized by complete absence of kidney development and is often accompanied by an absent ureter [55]. Four theories have been proposed as the cause: (i) failure of the metanephric bud to appear in spite of a normally preceding mesonephros, (ii) early regression of the metanephros, (iii) imperfect development of mesonephros and (iv) non-development of pronephros leading to non-growth of mesonephros [56].

Renal agenesis is usually unilateral with the prevalence of 1 in 1500–3200 live births and more common in males [57]. Bilateral renal agenesis is invariably fatal. URA is often asymptomatic and is incidentally diagnosed by radiology [58, 59]. The mean age at diagnosis for renal agenesis is 2.8 years [60]. This anomaly is more common on the left side. An exception to this left-sided predominance is noted in females with combined genital anomalies and URA that commonly presents on the right side [61]. The mechanisms leading to this lateralization remain unclear. Nearly half of the patients with URA have associated urological anomalies, VUR being the commonest [62]. This disorder is often associated with ipsilateral absence of the vas deferens in men and hypoplasia of the uterine horn in women. Renal agenesis has also been associated with chromosomal abnormalities such as 21, 22, 7 and 10 trisomies, 45 X mosaicism and 22q11 microdeletion [63].

A review of 30 cases with a congenital solitary functioning kidney revealed an absent left kidney (67%), associated anomalies that include the ear, nose and throat (30%), the musculoskeletal system (27%),

urological tract (47%), gastrointestinal tract (23%), cardiovascular (13%), dermatological and gynaecological (3%) anomalies. Proteinuria was observed in 20% and hypertension in 7% of patients. Chronic kidney disease was documented in 20% [64].

Syndromes with renal agenesis

1. Branchio-oto-renal syndrome (Melnick-Fraser syndrome): this autosomal dominant disease is characterized by coexistence of deafness, branchial fistulae, pre-auricular pits and renal anomalies, unilateral agenesis being more common. Most common mutation is present on EYA (Eyes-absent homologue 1) gene in chr 8q but also involves SIX1 and SIX6 genes [65–67]. The prevalence is 1: 40 000–70 000 [68].
2. Renal coloboma syndrome (papillorenal syndrome): it is characterized by renal hypoplasia and agenesis, vesicoureteral reflux and optic nerve coloboma [22] and is due to mutations in nuclear transcription factor PAired-boX gene 2 (PAX2) in chr 10q. Almost all patients develop end-stage kidney disease [69, 70].
3. Alagille syndrome (arteriohepatic dysplasia): marked arterionephrosclerosis with diffuse calcinosis, URA, vertebral anomalies (butterfly vertebrae), peripheral pulmonary stenosis, mental and growth retardation and neonatal cholestasis. This occurs due to mutations in NOTCH2 in chr 1p and JAG1 (Jagged 1) in chr 20p [71–74].
4. Winter syndrome: renal agenesis (unilateral/bilateral), middle-ear anomalies and internal genital malformations are noted in these patients. The mutation of the PAX-8 gene in chr 2q has been postulated [75].
5. Kallmann syndrome: URA, congenital anosmia, hypogonadism and cryptorchidism due to mutations in KAL1 in chr Xp [76].
6. CHARGE association: URA, duplicated upper pole of one kidney, coloboma, choanal atresia, cardiac, genital and ear defects are due to mutations in CHD7 (chromodomain helicase DNA-binding protein 7) in chr 8q [77].

Genetic testing

The benefit of genetic testing of patients and their relatives is not clear because of a general concern about the appropriateness and limitations of genetic testing in CAKUT. According to the standard guidelines, an appropriate genetic test should be accurate to identify a particular disease, which in most cases of CAKUT is not possible. This is due to uncertain phenotypical presentation and penetrance [3]. Thus, CAKUT is diagnosed through studying the foetal and postnatal imaging. Our knowledge of the genetic basis is mainly based on syndromic cases of CAKUT and animal models [78–80]. Genetic analyses are available only on a research basis [81].

Conclusions

The presence of one congenital anomaly is an indirect indicator of abnormalities in the other systems. Early diagnosis and treatment of urological anomalies are important to improve the long-term renal prognosis. Evaluation is advocated to patients with congenital

skeletal deformities of the extremities for co-existing renal anomalies. Parental counselling is necessary in case of genetically determined syndromes. Specialized outpatient clinics for rare diseases are increasingly common and patients should seek out these institutions.

Conflict of interest statement. None declared.

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